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National Cancer Institute
Bethesda, Maryland 20892

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket # 01D-0489

Dear Sir:

Enclosed are comments on the FDA draft "Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees".

Sincerely,

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Problems with the Draft FDA Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees (11/2001) : A DCTD and DCP Perspective

The Division of Cancer Treatment and Diagnosis (DCTD) and the Division of Cancer Prevention (DCP) of the National Cancer Institute sponsor numerous phase III multisite trials through the NCI Cooperative Group system which is of a different scope than a particular industry sponsor that might sponsor a small number of trials at limited number of institutions. In addition, the potential for conflicts of interest are obviously quite different for a government sponsor as compared to an industry sponsor. Because of these differences, the Draft Guidance raises serious concerns if applied to DCTD or DCP sponsored trials. We describe a number of these concerns, along with suggested changes to the document to lessen potential harm to publicly funded research through DCTD or DCP.

Problem : Applicability of the document

The document notes in section 1.2 that the potential conflicts of interest are “somewhat different” for government and industry sponsors. However, the rest of the document does not explicitly identify recommendations that would not be appropriate for government sponsors, and in fact might have negative consequences if followed by government sponsors. This leaves DCTD and DCP in the awkward position of trying to guess the FDA’s position on which statements should apply when DCTD or DCP is the sponsor.

Proposed solution:

For each statement in the guidance that has different implications for government and industry sponsors, separately clarify these statements in the guidance, e.g., “for industry sponsors,” and “for government sponsors, ...”.

Problem: Definition of “sponsor” in the document

Section 1 states “In this document, references to the sponsor with regard to trial management and decision-making should be understood to refer also to any individual or group to which the sponsor has delegated the relevant management responsibilities”. There are two problems with this. The first is that it does not explicitly consider the situation in which a government representative serves as a DMC member to protect the public’s interest in publicly supported research, but does not share his DMC-obtained information and decision-making with other individuals in the government. This is the situation for DCDT and DCP representatives to the DMCs of the Cooperative Groups, who sign confidentiality agreements to ensure this. By the definition in the guidance, this person would be considered the sponsor. This situation is not distinguished from that in which a sponsor representative freely shares his DMC-obtained information and decision-making with other individuals in the sponsoring organization. The

second problem is the wide scope of this definition. For example, the Cooperative Groups are funded by NCI (as part of cooperative agreements) to design and conduct clinical trials. A Cooperative Group funds, or partially funds, statisticians to work on these trials; these statisticians may also have academic appointments. Are these statisticians also to be considered the “sponsor”? The Draft Guidance would seem to suggest the answer is “yes.” In fact, it would appear that anyone working on the trial could be considered the sponsor.

Proposed solution:

For government sponsors, we suggest that the word “sponsor” be used only to refer to an individual when that individual is freely sharing the relevant management activity with other individuals in the government. For other situations, the document should specify explicitly what the relationship is, e.g., a government employee who is performing the activity as an individual with public interest responsibilities and with confidentiality agreements in place.

Problem: Independence of statistician analyzing data

The document states in various places that the statistician analyzing the ongoing trial should be independent of the sponsor and investigators (section 4.2.1, 4.3.1.4, and 6.4). We understand FDA’s concern about this as expressed in the document and at the meeting on 11/27/01: that changes to the trial design may be made by individuals with access to unblinded interim trial results. However, there would be significant, if not insurmountable, logistical difficulties for the hundreds of trials sponsored by the NCI to find additional sets of statisticians external to the trial development to perform high quality interim analyses. (An industry sponsor who is sponsoring a very limited number of trials may be able to do this.) In addition, the requirement for external statisticians may compromise patient safety, as the study statistician, who has helped design the trial, is in the best position to perform the interim analyses. Furthermore, study statisticians working with the Cooperative Groups funded by NCI are professionals with no financial interests in the results of the trials (perhaps unlike industry sponsors); thus, it is in their interest to avoid any action that would affect negatively the reliability of the trial results. Finally, for a DCTD or DCP sponsored trial it would be unlikely for a change to be made to the trial that was at all related to blinded interim results, as DMCS would likely not approve such an amendment due to its compromising the validity of the trial results. Thus, in trying to address a very rare problem with very limited potential negative consequences in the setting of government-sponsored clinical trials, the FDA is suggesting a solution that would interfere with the government being able to sponsor clinical trials conducted safely and with high quality.

Proposed solution:

For government sponsored trials, the FDA should not apply this level of independence for statisticians analyzing interim trial results. Instead, they could include a sentence in the Guidance such as “For government sponsored trials, the benefits of having the statistician performing interim analyses being the study statistician outweigh any perceived independence

issues. However, in the unlikely event that the trial is modified by individuals with access to blinded interim data in such a way that the modification could have been affected by the blinded interim data, then the FDA will take this potential bias into account when evaluating the evidence provided by the trial.”

Problem: Independence of the DMC with respect to NCI members

The DMCs of the Cooperative Groups have NCI participants as non-voting members, and these members offer important statistical and clinical expertise to the DMCs, as well as providing NCI oversight that the DMCs are operating properly in the public interest. In theory, expertise provided by these members could be provided by additional non-NCI members to the DMCs. However, given the hundreds of trials being monitored, this may not be easy. In addition, one would still require the NCI observers in order to provide their oversight. Note that reasons in section 6.1 for the desirability of not having sponsor members on the DMCs do not apply when NCI is the sponsor for Cooperative Group trials. In particular, (1) “sponsor interests” in publicly supported research should be the same as the DMC and public interests, (2) if changes are made to the trial, they are initiated by the Cooperative Group and not NCI, and (3) NCI does not have “business considerations”.

Proposed solution:

Clarify that DMCs can have NCI members provided that the NCI members do not share confidential information with anyone outside of the DMC. A less satisfactory solution, but still better than the recommendations in the Draft Guidance, would be to allow nonparticipating NCI observers to the DMC process.

Problem: Independence of the DMC with respect to Cooperative Group members

The DMCs of the Cooperative Groups have some Cooperative Group members, but the NCI Cooperative Group guidelines state that a majority of the voting members must be from outside the Group. We recognized when developing the Cooperative Group guidelines that there would be some benefits to not having any Group members on the DMC. However, since serving on a Cooperative Group DMC that is monitoring 20 trials can be a fair amount of work, it can be difficult to find enough qualified DMC members. Allowing some (but less than half) Cooperative Group members on the DMCs was a practical solution. Note that the members of the DMC sign conflict of interest statements to ensure they have no financial interests in the trials, so the situation is quite different than industry trials. Also, the Cooperative Group guidelines state that Cooperative Group members to the DMC should see themselves as primarily representing patient interests and not Group interests, and keep all information confidential (i.e., it is not shared with other members of the Cooperative Group).

Proposed solution:

Clarify that DMCs can have Cooperative Group members, provided they sign conflict of interest statements, and provided that they are less than a majority of the total voting DMC membership.

Problem: Trial leadership and not DMCs making changes to the trial

The Draft Guidance states that trial leadership and not the DMCs should be making changes to trials (sections 2.3 and 4.4.1.4) other than those driven by safety concerns. We understand that the FDA is addressing the concern about changes to the trial design being influenced by interim results. However, they are missing the bigger concern that trial leadership has a potential conflict of interest in making changes to the trial design. For example, suppose the accrual to a trial is very slow and much less than anticipated. Because of this the trial may never yield any meaningful results and it may be advisable to stop the trial. The trial leadership may have an inclination not to stop the trial because of the time they have already invested in it and because they may be over-optimistic about the chances of accrual increasing in the future. The DMC, on the other hand, has no potential conflicts of interests and is therefore in a better position to consider both the safety of the trial participants and the validity of the trial results. Because of these concerns, the NCI Cooperative Group guidelines state that all major changes to the protocol must be approved by the DMC.

Proposed solution:

Change the Guidance so that all major changes to the trial must be approved by the DMC.

Problem: Review of protocol by DMC

The Draft Guidance states that the DMC should review the statistical approach of the trial before it begins (section 4.3.2), and some speakers at the 11/27/01 meeting suggested they should also review other aspects of the protocol, e.g., the informed consent. Given the time and effort it requires to be on a DMC reviewing 20 trials, we believe best to have DMCs only do what others cannot do. In particular, the statistical approach to a NCI-sponsored Cooperative Group trial will have undergone multiple levels of review. (There seems to be some confusion at the FDA concerning this issue. The example given by an FDA speaker on 11/27/01 concerning this issue involved a situation where information came to light during a trial suggesting a change in design, which is a completely different issue than a review of the protocol before it begins. However, the Guidance states the DMC should not participate in such changes in an ongoing trial. As stated above, we believe changes to the design during the trial should be approved by the DMC.)

Proposed solution:

Remove from the Draft Guidance any statements that suggest the DMC should review protocols before they begin. Add to the document a statement that in the unlikely event that a particular DMC member objects to the design of a particular trial, and the member's objections cannot be addressed by the Study Committee or sponsor, he should recuse himself from participating in the

monitoring of that trial. Relevant to this issue, changes made to the protocol at a very early time point in a clinical trial can be made essentially in the absence of outcome data, thus providing an opportunity to negotiate changes in study design/analysis between the DMC and the sponsor without compromising trial validity.

Problem: Discussions with FDA

The Draft Guidance states that sponsors should discuss with the FDA certain changes to the trial suggested by the DMC before implementing them (section 7.3). This could significantly slow down the process in implementing changes to the trial, perhaps negatively impacting the safety of the participants or the validity of the trial. The Draft Guidance also implies that in some circumstances the FDA would routinely be getting interim trial results (section 5.2). Routine dissemination of interim trial results to individuals or groups is a bad idea; if the FDA wants to see interim results for a particular trial at a particular time they should make their request to the DMC (just as other groups that want to review interim data).

Proposed solution: Remove these statements from the document.

Problem: DMC Chair commitment

The document states that it is particularly important for the DMC Chair to commit to participate for the duration of the trial (section 4.1). For ongoing Cooperative Group DMCs that review many trials starting at different times, this would imply a life-long commitment.

Proposed solution: Add a statement to the effect that for DMCs that are monitoring many trials, DMC Chairs will need to be replaced at infrequent intervals.

Problem: DMC members entering subjects onto trials

The Draft Guidance states that this should not happen (section 4.1). However, any risk to the validity of the trial would be vanishing small if the trial were large and multi-institutional. As a practical matter, for some trials practically all the knowledgeable investigators will be potentially entering patients (e.g., some pediatric cancer trials). To have knowledgeable investigators on the DMC will require having members who are potentially entering subjects. We appreciate that physician DMC members may feel that their knowledge of interim results affects their ability to enter patients. For physicians with these concerns, there are various strategies that can be utilized (e.g., delegation to other staff at their institution discussions with patients and families concerning entry onto trials).

Proposed solution:

We would suggest adding a statement to the document similar to: “For large multi-institutional trials, practical considerations may require having DMC members who are entering some patients onto trials. DMC members who are in a leadership position for a particular trial should recuse themselves from participating in the monitoring of that trial.”

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